3. Studies of Cancer in Experimental Animals

The Working Group identified an issue that relates to the interpretation of several of the inhalation and intratracheal instillation studies of talc. A lesion that is frequently seen in rats that have been exposed by inhalation to a range of poorly soluble particles such as talc has been described variously as 'proliferating squamous cyst', 'proliferative keratinizing cyst', 'proliferating squamous epithelioma', 'benign cystic keratinizing squamous-cell tumour' or 'cystic keratinizing squamous-cell tumour'. Various authors have included this lesion in tumour counts, but the neoplastic nature of this lesion has been debated (Kittel *et al*., 1993; Carlton, 1994; Mauderly *et al*., 1994; Boorman & Seely, 1995; Rittinghausen *et al*., 1997; Rittinghausen & Kaspareit, 1998); its relationship to pulmonary neoplasia is uncertain.

The Working Group noted that, in many of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, that there was a lack of information on fibre content or particle size.

3.1 Oral administration

Rat

Groups of 25 male and 25 female Wistar rats, 10 weeks of age, received about 50 mg/kg body weight (bw) per day of commercial talc [characteristics unspecified] in the diet (average survival, 649 days) or standard di*et al*one for life (average survival, 702 days). No significant difference in tumour incidence was found in the treated animals compared with control animals (Gibel *et al*., 1976).

Groups of 16 male and 16 female Wistar-derived rats, 21–26 weeks of age, were fed 100 mg Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) per day per rat in the diet for 5 months (talc-containing diet was actually given for 101 days) and were then maintained on basal diet for life (average survival, 614 days). No differences in tumour incidence were noted between treated animals and eight male and eight female control animals fed basal diet throughout (average survival, 641 days) (Wagner *et al*., 1977). [The Working Group noted the limited exposure period and the advanced age of the animals at the start of the study.]

3.2 Inhalation exposure

3.2.1 *Mouse*

Groups of 47–49 male and 48–50 female B6C3F$_1$ mice, 7 weeks of age, that were fed an NIH-07 diet, were exposed by inhalation to aerosols containing 0, 6 or 18 mg/m^3 MP 10–52 grade talc for 6 hours per day on 5 days per week for up to 104 weeks (dose equivalent, 0, 2 or 6 mg/kg bw per day for male mice and 0, 1.3 or 3.9 mg/kg bw per day for female mice). MP 10–52 grade is a high-purity microtalc (from a strip mine located in Missouri State, USA) that has a maximal particle size of 10 μm and is reported to contain no tremolite or any asbestiform minerals. After analysis, the talc was found to be free of asbestos and almost free of silica. The average mass mean aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) of the talc aerosols were calculated to be 3.3 ± 1.9 μm and 3.6 ± 2.0 μm for the 6- and 18-mg/m^3 chambers, respectively. At approximately week 70, difficulties were experienced in generating the talc aerosol, and the chamber concentrations were substantially lower than the target concentrations over a period of 12 weeks. Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls, and no clinical findings were attributed to exposure to talc. No significant increases in the incidence of neoplasms were observed. The incidence of pulmonary neoplasms (males: 27%, 11% and 23%; females: 11%, 12% and 6%) was similar between exposed and control groups of mice. [The Working Group noted that the incidence of alveolar/bronchiolar adenoma or carcinoma combined in historical control B6C3F$_1$ mice fed an NIH-07 diet in National Toxicology Program inhalation studies was 26.8% for males and 10.1% for females] (National Toxicology Program, 1993).

3.2.2 *Rat*

Two groups of 12 male and 12 female Wistar-derived rats, 6–8 weeks of age, were exposed by inhalation to a mean respirable dust concentration of 10.8 mg/m^3 Italian talc (grade 0000; ready milled; mean particle size, 25 μm in diameter; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) for 7.5 hours per day on 5 days a week for 6 or 12 months (cumulative exposures, 8200 and 16 400 mg/m^3 × h, respectively). Ten days after the end of each exposure period, six rats per group were killed; 12 rats per group died and two rats per group were unaccounted for; the remaining four rats per group were killed 1 year after the end of the exposure period. No differences were noted in the incidence of lung tumours compared with 24 male and 24 female untreated controls (Wagner *et al.*, 1977). [The Working Group noted the limited number of animals allowed to survive longer than 12 months after the end of each exposure period.]

Groups of 49 or 50 male and 50 female Fischer 344/N rats, 6–7 weeks of age, were exposed by inhalation to aerosols of 0, 6 or 18 mg/m^3 MP 10–52 grade talc (see Section 3.2.1) for 6 hours per day on 5 days per week until mortality in any exposure group

reached 80% (113 weeks for males and 122 weeks for females; dose equivalent, 0, 2.8 or 8.4 mg/kg bw per day for males GSD and 0, 3.2 or 9.6 mg/kg bw per day for females). The average MMAD and the GSD of the talc aerosols were calculated to be 2.7 ± 1.9 µm and 3.2 ± 1.9 µm for the 6- and 18-mg/m^3 chambers, respectively. At week 11, the chamber concentration for the 18-mg/m^3 group varied from approximately 30 to 40 mg/m^3 for a period of 7 weeks because of difficulties with the systems used to monitor aerosol concentration. In addition, at approximately week 70, difficulties were experienced in generating the talc aerosol for a period of 12 weeks during which the chamber concentrations were substantially lower than the target concentrations. The survival of treated male and female rats was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11- and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18- and 24-month interim evaluations and at the end of the lifetime study. Exposure to talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The principal toxic lesions observed included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia, squamous cysts and interstitial fibrosis of the lung. The authors considered that the squamous cysts represented a form of squamous metaplasia. The incidence of alveolar/bronchiolar adenoma and carcinoma (combined) in female rats was: control, 1/50 (carcinoma, 0/50); low-dose, 0/48; high-dose, 13/50 (carcinoma, 5/50) and was significantly greater ($P < 0.001$) in the high-dose group than in controls (carcinoma, $P = 0.028$). The incidence of pulmonary neoplasms in exposed male rats was similar to that in controls. Adrenal medulla pheochromocytomas (benign and malignant combined) occurred with a significantly positive trend in males (control, 26/49; low-dose, 32/48; high-dose, 37/47; $P = 0.007$) and females (control, 13/48; low-dose, 14/47; high-dose, 23/49; $P = 0.014$), and the incidence in the high-dose groups was significantly greater than that in controls ($P = 0.006$ for males, $P = 0.024$ for females). The incidence of malignant pheochromocytomas in females was: control, 0/48; low-dose, 1/47; high-dose, 10/49 ($P = 0.001$). Although adrenal medulla hyperplasia occurred with similar frequency among exposed and control females, the incidence of hyperplasia in exposed males was significantly lower than that in controls (National Toxicology Program, 1993). [The Working Group noted that some authors have indicated that stress and hypoxia may lead to a proliferation of chromaffin cells and eventually to pheochromocytomas. An increase in the incidence of these tumours was also observed in several other National Toxicology Program studies that used particulates and the same rat strain in which the background incidence of this type of tumour was quite high (Ozaki *et al*., 2002; Melnick *et al*., 2003). The Working Group also noted that this type of tumour was not reported in particle inhalation studies other than those of the National Toxicology Program, and hence felt that this increase may not be related to talc.]

3.2.3 *Hamster*

In a lifetime experiment, three groups of 50 male and 50 female Syrian golden hamsters, 4 weeks of age, were exposed by inhalation to an aerosol of talc baby powder that was prepared from Vermont talc by flotation (95% w/w platy talc with trace quantities of magnesite, dolomite, chlorite and rutile) for 3, 30 or 150 minute per day on 5 days a week for 30 days. The mean aerosol concentration was 37.1 mg/m^3, with a measurable respiratory fraction of 9.8 mg/m^3 and a MMAD of 4.9 µm. A sham-exposed group comprised 25 males and 25 females. Two further groups of hamsters, 7 weeks of age, were exposed to talc aerosol for 30 or 150 minute per day for 300 days. The mean aerosol concentration was 27.4 mg/m^3, with a measurable respiratory fraction of 8.1 mg/m^3 and a MMAD of 6.0 µm. Another sham-exposed group comprised 25 males and 25 females. The survivors of the last two talc-exposed groups were killed at the age of 20 months. At that time, 20% of the males were still alive and all females were dead. No primary tumours were observed in the lungs in any of the hamsters, although the incidence of alveolar-cell hyperplasia in the groups given talc aerosol for 30 or 150 minutes per day for 300 days was 25% compared with 10% in the control group (Wehner *et al*., 1977, 1979). [The Working Group noted the short daily exposure time and the high mortality rate.]

3.3 Intratracheal administration

Hamster

Four groups of 24 male and 24 female Syrian golden hamsters, 9 weeks of age, received 18 weekly intratracheal instillations of 3 mg talc (USP grade; silica oxide, 61–63%; magnesium oxide, 32–34%; other dusts, 0.85–1.06%; 93.3% < 25 µm in diameter) in 0.2 mL saline with or without 3 mg benzo[*a*]pyrene, or 0.2 mL saline alone or were untreated. The animals were allowed to live out their lifespan (average 50% survival, 46–55 weeks). No respiratory tract tumours were observed in the talc-treated, saline-treated or untreated groups. Malignancies were observed in 33/45 animals treated with talc plus benzo[*a*]pyrene (Stenbäck & Rowlands, 1978). [The Working Group noted the short survival of the animals.]

3.4 Subcutaneous administration

Mouse

Fifty female R3 mice, 3–6 months of age, were given single subcutaneous injections of 0.2 mL of a mixture of 8 g talc [type unspecified] and 20 g peanut oil (delivered dose, about 80 mg) and were observed for life (average 50% survival, 596 days). No local tumour was observed (Neukomm & de Trey, 1961).

In a study reported in an abstract, female Marsh mice, 3 months of age, received single subcutaneous injections of 20 mg USP talc and were observed for 18–21 months. No tumour developed at the injection site in 26 treated animals or in 24 saline-injected controls (Bischoff & Bryson, 1976).

3.5 Intraperitoneal administration

3.5.1 *Mouse*

In a study that investigated the response to intraperitoneally injected asbestos, control groups of 12, four, five, six, five and 12 white male mice [age unspecified] were injected intraperitoneally with a 0.5-mL suspension (50%) of talc in saline and killed 26, 57, 112, 147, 170 and 343 days after injection, respectively. Talc was described as 6505–147–0000 Talc, USP V (no further analysis was made). Histopathological examination was performed, and no mesotheliomas or other neoplasms were reported (Jagatic *et al.*, 1967).

In a study reported as an abstract, female Marsh mice, 3 months of age, received a single intraperitoneal injection of 20 mg USP talc and were observed for 18–21 months. Intraperitoneal lymphoid tumours occurred in 5/22 treated animals and in 6/28 saline-treated controls (Bischoff & Bryson, 1976).

Fourty Swiss albino mice [sex unspecified], 6 weeks of age, received a single intraperitoneal injection of 20 mg ground commercial talc [type unspecified] in 1 mL saline. Within 6 months, 16 animals had died. In the 24 survivors allowed to live out their normal lifespan, three peritoneal mesotheliomas were observed, compared with 3/46 saline-treated controls (Özesmi *et al.*, 1985). [The Working Group noted the occurrence of mesotheliomas in saline-treated animals.]

3.5.2 *Rat*

A group of 40 female Wistar rats, 8–12 weeks of age, received four intraperitoneal injections of 25 mg granular talc [characteristics unspecified] in 2 mL saline at weekly intervals. A group of 80 female rats was injected with 2 mL saline alone and served as controls. The rats were observed until spontaneous death or when killed in moribund state. A mesothelioma was observed in 1/36 talc-exposed rats after 587 days compared with none in 72 controls (Pott *et al.*, 1974, 1976a,b).

In a study reported as an abstract, female Evans rats, 3 months of age, received a single intraperitoneal injection of 100 mg USP talc and were observed for 18–21 months. Of the treated rats, 3/27 developed tumours (one lymphosarcoma and one reticulum-cell sarcoma in the peritoneal cavity, one cystadenoma of the liver) compared with none of 26 saline-treated controls (Bischoff & Bryson, 1976).

3.6 Intrapleural and intrathoracic administration

3.6.1 *Mouse*

In a study reported as an abstract, male Marsh mice, 3 months of age, received a single intrathoracic injection of 10 mg USP talc. After 18–21 months, 5/47 treated mice had tumours (two adenocarcinomas and three lymphoid tumours of the lung) compared with none of 48 saline-injected controls (Bischoff & Bryson, 1976).

3.6.2 *Rat*

In a study reported as an abstract, female Evans rats, 3 months of age, received single intrathoracic injections of 50 mg USP talc. After 18–21 months, intrathoracic reticulum-cell sarcomas or lymphomas were observed in 7/30 talc-treated rats, 8/32 saline-treated rats and 7/28 untreated controls (Bischoff & Bryson, 1976).

In a lifetime study, a group of 24 male and 24 female Wistar-derived rats, 8–14 weeks of age, received a single intrapleural injections of 20 mg Italian talc (grade 00000; ready milled; mean particle size, 25 µm; containing 92% talc, 3% chlorite, 1% carbonate minerals and 0.5–1% quartz) in 0.4 mL saline. The mean survival time of the treated rats (655 days) was similar to that of 24 male and 24 female controls (691 days) that were injected with saline. No mesothelioma was detected in either group; one small pulmonary adenoma was found in one treated rat that died 25 months after injection (Wagner *et al.*, 1977).

Following thoracotomy, groups of 30–50 female Osborne-Mendel rats, 12–20 weeks of age, received intrapleural implantations of 40 mg of one of seven grades of refined commercial talc from separate sources in hardened gelatin. The rats were followed for 2 years, at which time survivors were killed. The incidence of pleural sarcomas was: talc 1, 1/26; talc 2, 1/30; talc 3, 1/29; talc 4, 1/29; talc 5, 0/30; talc 6, 0/30; talc 7, 0/29; untreated controls, 3/488 (0.6%); and controls that received implants of 'non-fibrous' materials described by the authors as 'non-carcinogenic', 17/598 (3%) (Stanton *et al.*, 1981).

3.7 Ovary implantation

Rat

In a study that investigated the effect of implanted talc on the rat ovary, a group of 10 female Sprague-Dawley rats, 10–15 weeks of age, received implants of 100 µL of a talc suspension in saline (100 mg/mL) onto the surface of the ovary by intrabursal injection. The talc was described as Italian 00000 (particle size, 0.3–14 µm) and contained no asbestos. Three sham-operated and three sham-treated control animals were included. Animals were killed after 12 months and histopathological examination of the ovaries was performed. Small focal areas of papillary change that were considered to be

preneoplastic changes were seen in the surface epithelium of 4/10 treated animals (0/6 controls). No neoplasms were reported (Hamilton *et al*., 1984). [The Working Group noted that groups of animals implanted for 1, 3, 6 or 18 months were also included, but no results were reported for any of these groups.].

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4. Mechanistic and Other Relevant Data

The general principles of inhalation, deposition, clearance and retention of poorly soluble particles that have low toxicity are discusssed in the Monograph on carbon black in this volume.

4.1 Humans

4.1.1 *Deposition, retention and clearance*

Talc particles have been found at autopsy in the lungs of patients with 'talc pneumoconiosis' (Schepers & Durkan, 1955a; Seeler, 1959; Kleinfeld *et al.*, 1963; Abraham & Brambilla, 1980; Berner *et al.*, 1981; Vallyathan & Craighead, 1981). Talc, in the form of platy or elongated particles, has been found at autopsy in the lungs of urban residents, farmers and asbestos miners (Seeler, 1959; Langer *et al.*, 1971; Pooley, 1976; Gylseth *et al.*, 1984). Talc has been reported to be concentrated in lung scar tissue (Yao *et al.*, 1984). Clinically, intrapleural instillation of talc is used to induce pleural adhesions in cases of pleural effusion and pneumothorax (Rodriguez-Panadero & Antony, 1997).

Churg and Wiggs (1985) used transmission electron microscopy and energy dispersive X-ray spectroscopy to analyse the total fibrous and non-fibrous mineral content of the lungs of a group of 14 male smokers who had lung cancer but no history of occupational exposure to dust. A group of 14 control men were matched by age, smoking history and general occupational class. The average concentrations of mineral fibres and non-fibrous particles were nearly fourfold and approximately twofold higher, respectively, in the group with cancer than in the controls. Kaolinite, talc, mica, feldspars and crystalline silica comprised the majority of fibrous and non-fibrous particles in both groups.

In a subsequent study, Churg and Wiggs (1987) examined the distribution of mineral fibres in the lungs of 10 male smokers who did not have lung cancer or a history of occupational exposure to dust. The subjects were all over 50 years of age at death and had a smoking history that ranged from 15 to 100 pack–years (mean, 45±24 pack–years). The primary minerals identified were kaolinite, silica and mica and accounted for 64% of the fibres; feldspars and talc accounted for 9 and 7%, respectively. There was a significant correlation between smoking history and particle concentration (number of particles per gram of tissue) in the upper lobes. The diameters (mean±standard deviation [SD]) of talc particles in the upper and lower lobes were 1.2±0.9 µm and 0.9±1.0 µm, respectively.

Dumortier *et al.* (1989) used analytical electron microscopy to examine non-fibrous particle content in the bronchoalveolar lavage fluid of 51 occupationally

exposed subjects, six of whom were talc millers. In the latter group, two workers had almost exclusively talc in their lavage fluid, while the others had about 60% talc and 40% chlorite. In other workers, talc generally accounted for <3% of the particles in lavage fluid. It was noted that, although the exposure of one of the millers had ceased 21 years before the examination, talc particles were still present in his lavage fluid.

Talc particles have been found in stomach tumours from Japanese men (Henderson *et al.*, 1975), possibly due to ingestion of talc-treated rice (Merliss, 1971a,b). Talc particles, but apparently no other insoluble particles, were found in the subserosal stroma of hernia sacs, possibly due to ingestion of medications in which talc is present as a filler (Pratt *et al.*, 1985). Anani *et al.* (1987) reported the presence of talc fibres in the intestinal wall of a 46-year-old patient who had severe intestinal pain and was diagnosed with intestinal talcosis. A possible source of exposure was the talc contained in oral medications against tuberculosis, which the patient had taken nearly 20 years earlier over a period of 22 months (total intake of talc, 183 g).

Talc is often present as a filler in some materials used by drug addicts, which results in wide dissemination of talc particles to the lungs (Groth *et al.*, 1972; Lamb & Roberts, 1972; Farber *et al.*, 1981; Crouch & Churg, 1983), spleen, kidney, liver, brain, heart, adrenal and thyroid glands (Groth *et al.*, 1972) and even the retina (AtLee, 1972). In the lungs, most of the talc particles are found within the vessels of the alveolar walls, and are almost invariably associated with marked foreign-body granulomas (Crouch & Churg, 1983). The talc particles found in the lungs are larger after intravenous injection than after inhalation (Abraham & Brambilla, 1980) (see Section 4.1.2 for a discussion of the associated toxic effects).

In view of epidemiological evidence of a possible association between talc use for perineal hygiene and an increased risk for ovarian cancer (see Section 2), several studies have been conducted in women to determine potential retrograde movement of particles through the reproductive tract to the ovaries. These studies involved women who were about to undergo gynaecological surgery, mostly for diseases or complications of the reproductive tract and organs. Therefore, broad interpretations with regard to healthy women may be limited.

Egli and Newton (1961) found that inert carbon particles deposited in the vagina in two of three patients travelled to the fallopian tubes in about 30 minutes. De Boer (1972) concluded that Indian ink deposited below the level of the cervix is unlikely to travel quickly through the reproductive tract. In contrast, the findings of Venter and Iturralde (1979) and Mostafa *et al.* (1985) suggested that retrograde transport to the fallopian tubes is possible. Henderson *et al.* (1971) reported the actual presence of talc in histological specimens from 10 of 13 ovarian tumours, 12 of 21 cervical tumours and five of 12 normal ovarian tissues. Subsequently, Henderson *et al.* (1979) and Heller *et al.* (1996) provided further evidence of the presence of talc in the ovaries of women who had purportedly had perineal exposure to talc. However, in the latter study, no relation was found between talc-particle counts and reported perineal use of talc.

4.1.2 *Toxic effects*

The toxic effects of talc in humans are dependent on the route and dose of administration and the physicochemical properties of the talc. In addition, talc products commonly contain other potentially toxic minerals (see Section 1).

Talc pneumoconiosis is somewhat more prevalent and severe among people who are exposed to talc that contains asbestiform minerals than among those who are exposed to talc with no such impurities (Kleinfeld *et al.*, 1963). The form of this pneumoconiosis varies widely, from a simple asymptomatic type (Vallyathan & Craighead, 1981) to disabling conglomerate pneumoconiosis (Hunt, 1956; Graham & Gaensler, 1965; Miller *et al.*, 1971). Mixed-dust pneumoconiosis is frequently seen, including silicosis, asbestosis and occasionally other forms (Kleinfeld *et al.*, 1963; Mark *et al.*, 1979).

Several early reports described 'talcum powder granuloma' that arose from the use of talc on surgical gloves (reviewed in Eiseman *et al.*, 1947). Subsequent reports of cases have documented a variety of surgical complications, including adhesions, pseudotumours and sinus tracts that were attributable to exposure to talc (Lichtman *et al.*, 1946; Eiseman *et al.*, 1947; reviewed by Hollinger, 1990). Both skin granulomas and talc pneumoconiosis have been reported after liberal use of talc on the body (Tye *et al.*, 1966; Nam & Gracey, 1972; Wells *et al.*, 1979; Tukiainen *et al.*, 1984; Wehner, 1994).

Respiratory distress syndrome, which can be fatal, has been described in children following massive accidental inhalation of talcum powder (Cless & Anger, 1954; Molnar *et al.*, 1962; Lund & Feldt-Rasmussen, 1969; Gould & Barnardo, 1972) and in adult patients after talc pleurodesis (Rehse *et al.*, 1999).

A variety of pathological effects arise from the intravenous use by drug addicts of products that contain talc. These include micronuclear pulmonary opacities (Hopkins & Taylor, 1970; Arnett *et al.*, 1976; Waller *et al.*, 1980), angiothrombotic pulmonary hypertension (Wendt *et al.*, 1964; Paré *et al.*, 1979; Waller *et al.*, 1980) and conglomerate pulmonary lesions (Sieniewicz & Nidecker, 1980; Crouch & Churg, 1983). In addition, retinopathy, cerebral microembolization and granulomas of the liver, lymph nodes and kidneys have been reported (Min *et al.*, 1974; Paré *et al.*, 1979; Carman, 1985).

A series of cross-sectional studies reported from the New York State Department of Labour (Kleinfeld *et al.*, 1955, 1963, 1964, 1973) have documented talc pneumoconiosis in talc miners and millers, especially among tremolitic talc workers. The cases were associated with pleural plaques, restrictive or obstructive breathing disorders and decreased vital capacity of the lungs. The prevalence of disease was lower among those with lower cumulative exposure to dust and among those who processed granular rather than fibrous talc.

A series of cross-sectional studies that described talc pneumoconiosis in workers in talc mining, milling and manufacture in Italy (Rubino *et al.*, 1963; Tronzano *et al.*, 1965) found that the prevalence was related to extent and duration of exposure and that talcs contaminated with tremolite, serpentine and quartz were associated with significant pneumoconiosis.

One representative, well-controlled study among 80 workers exposed in the rubber industry to Vermont talc, which is reported to have a low content of silica and fibres, showed significantly increased respiratory symptoms, impaired ventilatory function and increased respiratory morbidity, but no radiographic abnormality (Fine *et al*., 1976).

There has been some concern that talc may cause adult respiratory distress syndrome when instilled into the pleural space for pleurodesis (Rinaldo *et al.*, 1983; Bouchama *et al.*, 1984; Kennedy *et al.*, 1994; Rehse *et al.*, 1999; Light, 2000). Relatively recent cases were observed when talc was both insufflated and used as a slurry (Brant & Eaton, 2001; Scalzetti, 2001). However, other case series did not report the development of this disease (Weissberg & Ben-Zeev, 1993; Rodriguez-Panadero & Antony, 1997; Sahn, 2000; Ferrer *et al.*, 2001, 2002; Cardillo *et al.*, 2006). Many of the patients in the case reports had co-morbid conditions. [The Working Group noted that the talc used in these reports was not always characterized mineralogically and may have contained contaminants.]

The role of exposure to talc in the development of ovarian cancer has raised concerns (see Section 2). The normal ovarian epithelium is known to express several mucins that are protective against epithelial inflammation and injury (Lalani *et al.*, 1991; Gipson *et al.*, 1997; Ness & Cottreau, 1999; Taylor-Papadimitriou *et al.*, 1999; Ness *et al.*, 2000; La Vecchia, 2001). Several epithelial cancers, such as breast and ovarian cancer, express mucin (MUC-1) which is upregulated and aberrantly glycosylated in many carcinomas (Taylor-Papadimitriou *et al.*, 1999).

Cramer *et al.* (2005) examined the association between the characteristics of women with no previous diagnosis of ovarian cancer and levels of antibodies to MUC-1, a protein that is expressed by normal epithelial cells and overexpressed by ovarian cancer cells. The study participants were 705 controls from a case–control study of ovarian cancer conducted in Massachusetts and New Hampshire (USA) between 1998 and 2003. Plasma specimens collected from participants at enrolment into the study were analysed for anti-MUC-1 antibody levels using an enzyme-linked immunosorbent assay. Forty-eight cases of ovarian cancer with pre-operative blood specimens were also included in additional analyses; further 668 cases of ovarian cancer were included in the analyses to evaluate risk factors for ovarian cancer. Multivariable logistic regression, Spearman rank correlations and generalized linear models were used in the statistical analyses to determine which characteristics were associated with anti-MUC-1 antibody production and which were associated with the risk for ovarian cancer. Women who reported no previous genital use of talc were more likely to have antibodies to MUC-1 than women who had a history of regular genital exposure to talc (38.1% versus 28.6%; $P = 0.04$). In addition, there was a borderline significant trend between frequency of talc use and lower anti-MUC-1 antibody levels ($P = 0.11$), after adjustment for other characteristics that affect antibody levels. Several conditions associated with increased antibody production were associated with a decreased risk for ovarian cancer. The authors concluded that these findings suggest that the presence of anti-MUC1 antibodies is inversely correlated with risk for ovarian cancer. [Limitations of this study included the potential for bias in the participants' recollection of their genital use of talc, due to the case–control study design.

In addition, antibody levels in the cases and controls may not be comparable, since the presence of a cancer may affect anti-MUC-1 antibody levels.]

4.2 Experimental systems

4.2.1 *Deposition, retention and clearance*

The deposition, translocation and clearance of talc was investigated in 44 female golden Syrian hamsters (10 weeks of age) that were exposed by nose-only inhalation for 2 hours to 40–75 mg/m^3 neutron-activated talc (Johnsons's Baby Powder®, lot 228p; median aerodynamic diameter, 6.4–6.9 µm). The powder was high-grade cosmetic talc and consisted of 95% (w/w) platy talc mineral (Wehner *et al.*, 1977a). Alveolar deposition was approximately 20–80 µg, which represented 6–8% of the inhaled amount. The retention half-time of the talc deposited in the alveoli was 7–10 days, and alveolar clearance was reported to be essentially complete 4 months after exposure. No translocation of talc to liver, kidneys, ovaries or other parts of the body was found (Wehner *et al.*, 1977b). [The Working Group noted that the unusually short clearance time may be related to limitations in the sensitivity of the detection methods and the large size of the particles used.]

In rats exposed for 7.5 h per day on 5 days a week to aerosols of Italian talc (mean concentration of respirable dust [not further defined], 10.8 mg/m^3), the mean amounts of talc retained in the lung were 2.5, 4.7 and 12.2 mg per animal following exposures for 3, 6 and 12 months, respectively. These levels were approximately proportional to the cumulative exposures (Wagner *et al.*, 1977). In rats exposed for 6 hours per day on 5 days a week for 4 weeks to 2.3, 4.3 and 17 mg/m^3 respirable talc, the amounts retained in the lung at the end of exposure were 77, 187 and 806 µg talc/g lung, respectively (Hanson *et al.*, 1985).

Lung burdens of talc were determined in groups of 10 male and 10 female Fischer 344 rats and B6C3F$_1$ mice following exposure to asbestos-free talc for 6 hours per day on 5 days a week for 4 weeks. In rats exposed to 0, 2.3, 4.3 and 17 mg/m^3, average lung burdens were 0, 0.07, 0.17 and 0.72 mg talc/g lung, respectively. In mice exposed to 0, 2.2, 5.7 and 20.4 mg/m^3, average lung burdens of 0, 0.10, 0.29 and 1.0 mg talc/g lung, respectively, were observed. When normalized to the exposure concentration, the lung burden in mice was greater than that in rats and the normalized burden in rats increased with increasing exposure concentration (Pickrell *et al.*, 1989).

Conflicting data exist on systemic distribution following intrapleural instillation of talc (i.e. talc pleurodesis) in rats. Following administration of 10 or 20 mg talc [particle size unspecified] to rats (20 per group), talc was identified in the chest wall, lungs, heart, brain, spleen and kidneys. The authors concluded that talc is rapidly absorbed through the pleura and reaches the systemic circulation and organs 24 hours after administration (Werebe *et al.*, 1999). However, following instillation of 40 mg talc (median particle size, 31 µm) into 33 rats randomly assigned to autopsy 24 or 72 hours later, talc particles were

observed in only a few extrapulmonary organs, i.e. the brain, spleen and liver, but not the kidneys (Fraticelli *et al.*, 2002).

The systemic distribution of talc was investigated in rabbits following talc pleurodesis in two studies. In one study (Ferrer *et al.*, 2002), 10 rabbits received 200 mg/kg bw 8.4-μm asbestos-free talc particles and 10 received 200 mg/kg bw 12-μm talc particles. Five animals from each group were killed after 24 hours and five at 7 days after instillation. A tendency was seen for increased extrapulmonary distribution of the smaller particles, which were identified in the pericardium of 0/5 and 3/5 rabbits at 24 hours and 7 days, respectively. For the larger particles, one of five animals had talc in the pericardium at each time-point. Particles were identified in the liver of three of five animals exposed to the smaller particles 7 days after instillation; other groups had no particles in the liver. Small particles were found in the kidney of only 1/5 animals 24 hours after instillation. Both particle types were found in the spleen of 1/5 animals 24 hours after instillation. The results indicate that talc reached the lung parenchyma by breaking the mesothelial and elastic layer and that mobility was greater for the smaller particles.

In the other study, Montes *et al.* (2003) performed talc pleurodesis in rabbits (20 per group) at doses of 50 and 200 mg/kg bw of the small-particle talc used in the study by Ferrer *et al.* (2002). Doses were chosen to simulate treatment of a 60-kg patient with amounts of 3 and 12 g talc. The lung parenchyma of two and 14 rabbits of the low-dose and high-dose groups, respectively, contained talc. In the high-dose group, six of the animals had talc in the pericardium and five had talc in the liver; talc was not detected in these organs in the low-dose group. The results show that the systemic distribution of talc was dose-dependent.

In studies in rats, mice, guinea-pigs and hamsters that used radioactive tracer techniques, no intestinal absorption or translocation of ingested talc to the liver or kidneys was detected (Wehner *et al.*, 1977b; Phillips *et al.*, 1978). No translocation of talc into the ovaries was detected after single or multiple intravaginal applications of talc to rabbits (Phillips *et al.*, 1978) or monkeys (Wehner *et al.*, 1985, 1986).

4.2.2 *Toxic effects*

Reviews of the literature on the biological effects of talc in experimental animals are available (Lord, 1978; Wehner, 1994).

[The Working Group noted that in most of the studies of 'talc' described below, no or limited characterization of the mineralogy of the sample employed was given, and, in particular, information on fibre content or particle size was lacking.]

(a) Chronic toxicity

Mild to marked arterial endothelial cell proliferation with cellular encroachment into the lumen, the occurrence of occasional foreign-body giant cells within the endothelial masses and moderate thickening of the intra-alveolar septa of the lungs were observed

after intravenous injections of talc in rabbits and guinea-pigs (Puro *et al.*, 1966; Dogra *et al.*, 1977). No effect on the rat lung was observed after intravenous injection of talc (Schepers & Durkan, 1955b) but talc granulomas were seen in rats following intrasplenic injection of talc (Eger & Canaliss, 1964).

No chronic pathological effect was associated with oral administration of Italian talc (92% pure; 100 mg per day on 101 days over 5 months) to rats (Wagner *et al.*, 1977). Intratracheal injections of talc (total dose, 150 mg) into guinea-pigs induced perivascular and peribronchiolar focal accumulations of histiocytes, fibrocytes, plasma cells and eosinophils within 1 month. After 2 years, the dominant effects were bronchiolectasia, bronchiolitis and marked fibrosis (Schepers & Durkan 1955b).

Rats exposed to dust clouds of 30–383 mg/m^3 'industrial'- or 'pharmaceutical'-grade talc for 9 months developed chronic inflammatory changes including thickening of the walls of the pulmonary arteries and, eventually, emphysema (Bethge-Iwańska, 1971).

In rats exposed by inhalation to 10.8 mg/m^3 Italian talc (grade 00000; ready milled; mean particle size, 25 μm) for 3 months, minimal fibrosis was observed, the degree of which did not change during the observation period after exposure. Animals that were exposed for 1 year had minimal to slight fibrosis, the degree of which had increased to moderate within 1 year after cessation of exposure (Wagner *et al.,* 1977). In contrast, Syrian golden hamsters exposed to 8-mg/m^3 aerosols of cosmetic-grade talc for up to 150 minutes per day on 5 days a week for 30 days showed no histopathological change in the lungs, heart, liver, renal tissues, stomach or uterus (Wehner *et al.,* 1977c).

Two years after injection of 20 mg Italian talc (see above) into the right pleural cavity of rats, granulomas at the injection site were common, and one small pulmonary adenoma was observed, but no other relevant pathology was seen in the lungs (Wagner *et al.*, 1977).

Groups of male and female rats, 6–7 weeks old, were exposed to aerosols of 0, 6 or 18 mg/m^3 talc until mortality in any exposure group reached 80% (113 weeks for males and 122 weeks for females). These exposure concentrations provided a dose equivalent of 0, 2.8 or 8.4 mg/kg bw per day for male rats and 0, 3.2 or 9.6 mg/kg bw per day for female rats. The talc used for this study was MP 10–52 Grade (see Section 3.2.1) and was found to be free from asbestos by polarized light microscopy and transmission electron microscopy. Survival of male and female rats was similar to that of the controls. Mean body weights of rats exposed to 18 mg/m^3 were slightly lower than those of controls after week 65. No clinical findings were attributed to exposure to talc. Absolute and relative lung weights of male rats exposed to 18 mg/m^3 were significantly greater than those of controls at the 6-, 11- and 18-month interim evaluations and at the end of the lifetime study, while those of female rats exposed to 18 mg/m^3 were significantly greater at the 11-, 18- and 24-month interim evaluations and at the end of the study. Talc produced a spectrum of inflammatory, reparative and proliferative processes in the lungs. The principal toxic lesions observed included chronic granulomatous inflammation, alveolar epithelial hyperplasia, squamous metaplasia, squamous cysts and interstitial fibrosis of the lung. These lesions were accompanied by impaired pulmonary function characterized

primarily by reduced lung volumes, reduced dynamic and/or quasistatic lung compliance, reduced gas-exchange efficiency and non-uniform intrapulmonary gas distribution (National Toxicology Program, 1993).

Groups of male and female B6C3F$_1$ mice, 7 weeks of age, were exposed by inhalation to aerosols that contained 0, 6 or 18 mg/m^3 MP 10–52 grade talc (see Section 3.2.1) for up to 104 weeks (dose equivalents, 0, 2 or 6 mg/kg bw per day for male mice and 0, 1.3 or 3.9 mg/kg bw per day for female mice). Survival and final mean body weights of male and female mice exposed to talc were similar to those of the controls. No clinical findings were attributed to exposure to talc. Inhalation exposure to talc was associated with chronic inflammation and accumulation of macrophages in the lung. Accumulations of macrophages (histiocytes) containing talc particles were also observed in the bronchial lymph nodes (National Toxicology Program, 1993).

(b) In-vitro toxicity

A concentration >50 μg/mL Italian talc caused a 50% reduction in the colony-forming efficiency of cultured Chinese hamster V79-4 lung cells (Chamberlain & Brown, 1978).

The concentration of talc (99% pure) required to cause 50% haemolysis of red blood cells was 6.5 mg/mL, which is more than 50-fold that of chrysotile. A concentration of 0.1 mg/mL talc caused 35% release of ^{51}Cr from Syrian hamster tracheal epithelial cells labelled with radioactive sodium chromate; the concentration was twofold that required for chrysotile (Woodworth *et al.*, 1982).

Davies *et al.* (1983) examined the effect of different types of talc on mouse peritoneal macrophages *in vitro*. Macrophages were exposed to seven specimens of high-purity talcs and the release of lactate dehydrogenase and β-glucuronidase was measured. These enzymes are produced by macrophages after they digest materials that can induce fibrosis and chronic inflammation. Enzyme release after exposure of macrophages to quartz, a known fibrogenic dust, and magnetite, a non-fibrogenic dust, was also measured. Quartz caused the greatest cytotoxic reaction *in vitro*: the amount of enzyme released increased with the dose. Magnetite had no effect. All seven talc specimens were cytotoxic to the macrophages: the levels of enzymes released were dose-related but were lower than those observed after exposure to quartz. The results show that talc is cytotoxic to macrophages and may be able to induce fibrosis and chronic inflammation in animals. However, the macrophage response to talc appears to be weaker than that for other fibrogenic dusts such as quartz, and the response of macrophages to talc may be different *in vivo*.

Talc caused the release of several cytokines including C-X-C and C-C chemokines from normal human pleural mesothelial cells (Nasreen *et al.*, 1998). Pleural mesothelial cells exposed to talc did not undergo apoptosis, whereas malignant mesothelioma cell lines (ATTC CRL-2081, CRL-5820, CRL-5915) exposed to the same dose did (Nasreen *et al.*, 2000). Talc also caused the release of basic fibroblast growth factor in pleural mesothelial cells (Antony *et al.*, 2004).

In bone marrow-derived macrophages from mice, talc was found to stimulate DNA synthesis ([^{3}H]thymidine incorporation) (Hamilton *et al.*, 2001).

4.2.3 *Genetic and related effects*

Three samples of respirable talc failed to elicit significant unscheduled DNA synthesis (10, 20 and 50 µg/cm^2, 24 hours), sister chromatid exchange or aneuploidy (2, 5, 10 and 15 µg/cm^2, 48 hours) in rat pleural mesothelial cells, in contrast to various positive controls. The three samples, i.e Spanish talc (No. 5725), Italian talc (No. 5726) and French talc (No. 7841), contained 90–95% talc; the remaining contents were chlorite and dolomite. Electron microscopy analysis revealed that talc particles were taken up by the rat pleural mesothelial cells, but no aneuploidy was observed in metaphases (Endo-Capron *et al.*, 1993).

4.3 References

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5. Summary of Data Reported

5.1 Exposure data

The term 'talc' refers to both mineral talc and industrial mineral products that contain mineral talc in proportions that range from about 35% to almost 100% and are marketed under the name talc. Mineral talc occurs naturally in many regions of the world where metamorphosed mafic and ultramafic rocks or magnesium carbonates occur. Mineral talc is usually platy but may also occur as asbestiform fibres. (Asbestiform refers to a habit (pattern) of mineral growth and not to the presence of other minerals. Asbestiform talc must not be confused with talc that contains asbestos.) Together with platy talc, asbestiform talc is found in the Gouverneur District of New York State, USA, and occasionally elsewhere; it may be associated with other minerals as observed by transmission electron microscopy.

Talc products vary in their particle size, associated minerals and talc content depending on their source and application. Minerals commonly found in talc products include chlorite and carbonate. Less commonly, talc products contain tremolite, anthophyllite and serpentine.

Mineral talc is valued for its softness, platyness, inertness and ability to absorb organic matter. It is used in agricultural products, ceramics, paint and other coatings, paper, plastics, roofing, rubber, cosmetics and pharmaceuticals and for waste treatment. Cosmetic talc, which contains more than 90% mineral talc, is present in many cosmetic products and is used for many purposes, including baby powders and feminine hygiene products. The type of talc that is currently used for cosmetic purposes in the USA does not contain detectable levels of amphibole, including asbestos. It is not known whether this is true in other countries.

Workers are exposed to talc during its mining and milling. Reported geometric mean exposure levels to respirable dust are typically in the range of 1–5 mg/m^3. Workers may also be exposed in user industries, primarily in the rubber, pulp and paper and ceramics industries. Due to the presence of other particulates, exposure levels may be difficult to measure accurately. Consumer exposure by inhalation could occur during the use of loose powders that contain talc.

Accurate estimates of prevalence are not available. However, in some series of controls from epidemiological studies of ovarian cancer, the prevalence of use for feminine hygiene of body powders, baby powders, talcum powders and deodorizing powders, most of which contain cosmetic talc in varying amounts, has been reported to be as high as 50% in some countries. Perineal use for such purposes seems to have been a common practice in Australia, Canada, the United Kingdom, the USA and other countries, including Pakistan. Use of cosmetic talc in the USA has declined steadily since the late 1970s.

5.2 Human carcinogenicity data

The carcinogenic effect of exposure to talc not contaminated by asbestos fibres has been investigated in five independent but relatively small cohort studies of talc miners and millers in Austria, France, Italy, Norway and the USA. The miners and to a lesser extent the millers in these cohorts were also exposed to quartz. In a case–control study nested in the combined cohorts of talc workers from Austria and France, there was no tendency of higher risks for lung cancer by increasing cumulative exposure of workers to talc dust. In four of five studies, it was explicitly stated that no case of mesothelioma was observed. In the two studies from Italy and Norway, which included an estimate of cumulative exposure of the cohort to talc dust, the risk for lung cancer in the highest category was found to be close to or below unity. In the subgroup of miners in the study in the USA, an excess risk for lung cancer was found, which may be have been due to exposure in the workplace to radon daughters and quartz. In all the other groups of workers studied, there was no increased risk for lung cancer.

Female workers in the Norwegian pulp and paper industry had an increased risk for ovarian cancer, which, however, was attributed to exposure to asbestos. A community-based case–control study did not find an increased risk for ovarian cancer associated with occupational exposure to talc, but the prevalence of exposure was low.

Body powder containing talc has been used by women on the perineum (or genital area), on sanitary napkins and on diaphragms. In total, data from one prospective cohort study and 19 case–control studies were reviewed in the evaluation of the association of cosmetic talc use and the risk for ovarian cancer. The information collected on perineal talc use varied substantially by study (e.g. ever use versus regular use, and whether information on the mode of application, frequency or duration of use was available).

The cohort study was conducted among nurses in the USA and included 307 cases of ovarian cancer that occurred over 900 000 person–years of observation and a maximum of 14 years of follow-up. Information was collected on the frequency but not duration of regular use. Perineal use of talc was not associated with a risk for ovarian cancer.

The 20 case–control studies were conducted in Australia, Canada, China, Greece, Israel, Norway, the United Kingdom and the USA (nested case–control study), and included between 77 and 824 cases and 46 and 1367 controls. Five were hospital-based designs and the others were population-based studies. The Working Group designated a subset of these studies as being more informative based on the following characteristics: the study was population-based, was of a reasonable size, had acceptable participation rates and included information to allow control for potentially important confounders.

Eight population-based case–control studies from Australia, Canada (Ontario) and the USA (two non-overlapping studies in Boston, MA, and one each in California, Delaware Valley, eastern Massachusetts and New Hampshire and Washington State) were thereby identified as being more informative. The selected studies included at least 188 cases and had participation rates that generally ranged from 60 to 75%. Among these eight studies, the prevalence of use of body powder among controls ranged from 16 to 52%; however,

information on exposure was not collected in a comparable manner across studies. In addition, the frequency and duration of use or total lifetime applications were investigated in several studies as well as consideration of prior tubal ligation or simple hysterectomy. Only sparse data were available on whether women had used body powder before or after the mid-1970s.

The relative risks for ovarian cancer among users of body powder (versus non-users) were homogenous across this relatively diverse set of eight studies, each of which indicated a 30–60% increase in risk. Among the other 11 case–control studies, most also reported relative risks of this magnitude or higher. The subset of studies that assessed use of talc on a diaphragm were relatively uninformative due to their lack of precision.

Results on exposure–response relationships were presented in the cohort study and in seven of the more informative case–control studies. In the cohort study, no exposure–response trend was apparent. Positive exposure–response trends were apparent in the two Boston-based studies that presented the most comprehensive analysis. In the Canadian and Californian studies, a non-significant, weakly positive trend was observed for either duration or frequency of use, but not for both. In the other three case–control studies, no consistent trend was observed and the strongest associations tended to be seen among the shorter-term or less frequent talc users.

The cohort study and four of the eight more informative case–control studies presented results on histological type of ovarian cancer. When the analysis of the cohort study was restricted to the 160 serous invasive cases, a statistically significant increase in risk of about 40% was observed. The risk increased with increasing frequency of body powder use. Risks for serous ovarian cancer were somewhat greater than those for other histological types in two of the four case–control studies in which the contrast was reported. Results for other histological types were inconclusive.

The Working Group carefully weighed the various limitations and biases that could have influenced these findings. Non-differential misclassification of talc use, given the relatively crude definitions available, would have attenuated any true association. Although the available information on potential confounders varied by study, most investigators accounted for age, oral contraceptive use and parity. In most studies, only the adjusted relative risks were presented; however, in the three studies in which both age-adjusted and fully adjusted estimates were provided, relative risks did not differ materially, suggesting minimal residual confounding.

It is possible that confounding by unrecognized risk factors may have distorted the results. One or more such factors, if they are causes of ovarian cancer and also associated in the population with perineal use of talc, could induce the appearance of an association between the use of talc and ovarian cancer where there is none. In order for such an unrecognized risk factor to induce the consistent pattern of excess risks in all of the case–control studies, it would be necessary for the factor to be associated with perineal talc use across different countries and different decades. While the range of countries and decades covered by the more informative case–control studies is not very broad, it provides some

diversity of social and cultural context and thereby reduces the likelihood of a hidden confounder.

There was a distinct pattern of excess risk discernible in all of the case–control studies when users were compared with non-users; however, methodological factors needed to be considered. First, while chance cannot be ruled out as an explanation, it seemed very unlikely to be responsible for the consistent pattern of excess risks. A second possible explanation would be recall bias, to which case–control studies may be particularly susceptible. This may have been the case if there had been widespread publicity about the possible association between the use of body powder and cancer. In such circumstances, it is possible that women who had ovarian cancer could be more likely than women who did not to remember or over-report a habit, such as body powder use, if they thought that it may have played a role in their illness..There was a flurry of publicity in the USA in the mid-1970s concerning the possible risks for cancer posed by the use of talc-based body powders. Following an industry decision to market talc powders with no asbestos, it was the opinion of the Working Group that there had not been widespread public concern about this issue, at least until very recently. Therefore, the Working Group considered it unlikely that such a bias could explain the set of consistent findings that stretch over two decades. The Working Group believed that recall bias was a possibility inherent in the case–control studies and could not be ruled out. The Working Group also considered publication and selection biases and these were not judged to have substantially influenced the pattern of findings.

The Working Group searched for documentation on the presence of known hazardous minerals in talc-based body powders. There were strong indications that these products contained quartz in the mid-1970s and still do. There were also indications that occasional small concentrations of asbestos were present in these products before the mid-1970s, but the available information was sparse, sampling methods and detection limits were not described, and the range of locations where data were available was extremely limited. As a result, the Working Group found it difficult to identify a date before which talc-based body powders contained other hazardous minerals and after which they did not, or to have confidence that this would be applicable worldwide. In addition, the epidemiological studies generally do not provide information about the years during which the female subjects were exposed. Consequently, the Working Group could not identify studies in which an uncontaminated form of talc was the only one used by study subjects. Nevertheless, the Working Group noted that, even in the most recent studies in the USA, where exposure histories may have been much less affected by hazardous contaminants of talc, the risk estimates were not different from the early studies in which the possibility of such exposure was more likely.

To evaluate the evidence on whether perineal use of talc causes an increased risk for ovarian cancer, the Working Group noted the following:

- The eight more informative case–control studies, as well as most of the less informative ones, provided overall estimates of excess risk that were remarkably consistent; seven of these eight case–control studies examined exposure–response

relationships; two provided evidence supporting such a relationship, two provided mixed evidence and three did not support an association.

- The cohort study neither supports nor strongly refutes the evidence from the case–control studies.
- Case–control studies were susceptible to recall bias which could tend to inflate risk estimates but to an unknown degree.
- All of the studies were susceptible to other potential biases which could either increase or decrease the association.
- All of the studies involved some degree of non-differential misclassification of exposure that would tend to underestimate any true underlying association.

5.3 Animal carcinogenicity data

Talc of different grades was tested for carcinogenicity in mice by inhalation exposure, intrathoracic, intraperitoneal and subcutaneous injection, in rats by inhalation exposure, intrathoracic injection, intraperitoneal injection, oral administration and intrapleural and ovarian implantation, and in hamsters by inhalation exposure and intratracheal injection.

In male and female rats exposed by inhalation to a well-defined talc, the incidence of alveolar/bronchiolar carcinoma or adenoma and carcinoma (combined) was significantly increased in female rats. The incidence of adrenal medulla pheochromocytomas (benign, malignant or complex (combined)) showed a significant positive trend and the incidence in high-dose males and females was significantly greater than that in controls. The incidence of malignant pheochromocytomas was also increased in high-dose females. The Working Group did not consider it probable that the increased incidence of pheochromocytomas was causally related to talc but, based on the experimental data available, neither could talc-related effects be excluded.

Tumour incidence was not increased following the intrapleural or intrathoracic administration of a single dose of various talcs to rats. In two studies of intraperitoneal administration in rats, no increase in the incidence of mesotheliomas was observed. No increased incidence of tumours was produced in rats in two studies of talc administered in the diet or in another study of the implantation of talc on to the ovary.

Tumour incidence was not increased in mice following the inhalation of talc in one study, the intrathoracic administration of a single dose of various talcs in another study or the administration of talc by intraperitoneal injections in three studies. A single subcutaneous injection of talc into mice did not produce local tumours.

Tumour incidence was not increased following inhalation or intratracheal administration of talc to hamsters.

5.4 Mechanistic considerations and other relevant data

Different mechanisms are probably operative in the effects of talc on the lung and pleura, depending on the route of exposure.

In humans, deposition, retention and clearance of talc have been insufficiently studied, although talc particles have been found at autopsy in the lungs of talc workers.

In humans and experimental animals, the effects of talc are dependent on the route of exposure, and the dose and properties of the talc. Talc pneumoconiosis was somewhat more prevalent and severe among miners exposed to talc containing asbestiform minerals and/or asbestos than among those exposed to talc without such contaminants. However, the role of quartz and asbestos in the observed pneumoconiosis could not be ruled out. Among drug users, intravenous injection of talc present as a filler in the drugs resulted in microembolization in a variety of organs and alterations in pulmonary function.

In animal studies, talc has been shown to cause granulomas and mild inflammation when inhaled. Observations of the effects that occurred in the lungs of rats exposed by inhalation to talc suggested that the operative mechanisms may be similar to those identified for carbon black, and talc is known to cause the release of cytokines, chemokines and growth factors from pleural mesothelial cells.

In humans, intrapleural administration of talc as a therapeutic procedure results in pleural inflammation which leads to pleural fibrosis and symphysis. Pleural fibrosis is the intended effect of intrapleural administration of talc in patients with malignant pleural effusions or pneumothorax. Animal studies suggested that extrapulmonary transport of talc following pleurodesis increases with decreasing particle size and increasing administered dose. Talc has been shown to cause apoptosis of malignant cells *in vitro*.

Perineal exposure to cosmetic talc in women is of concern because of its possible association with ovarian cancer. Several studies have been conducted in women to assess potential retrograde movement of particles through the reproductive tract to the ovaries. These have been conducted in women who were about to undergo gynaecological surgery, most of whom had diseases or complications of the reproductive tract and organs that required surgery. The findings reported in these studies may be confounded by the various levels of dysfunction in clearance from the female reproductive tract due to underlying pathologies. In addition, most of the studies had little or no further information on the use of talc products for perineal hygiene or changes in habits that may have preceded surgery. On balance, the Working Group believed that the evidence for retrograde transport of talc to the ovaries in normal women is weak. In women with impaired clearance function, some evidence of retrograde transport was found. Studies in animals (rodents, langomorphs and non-human primates) showed no evidence of retrograde transport of talc to the ovaries.

In one study, predictors of the presence of antibodies to mucin protein were inversely related to the risk for ovarian cancer and exposure to powder containing talc.

No data were available on the genotoxic effects of exposure to talc in humans. The limited number of studies available on the genetic toxicology of talc *in vitro* gave negative results.

6. Evaluation and Rationale

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of inhaled talc not containing asbestos or asbestiform fibres.

There is *limited evidence* in humans for the carcinogenicity of perineal use of talc-based body powder.

6.2 Cancer in experimental animals

There is *limited evidence* in experimental animals for the carcinogenicity of talc not containing asbestos or asbestiform fibres.

6.3 Overall evaluation

Perineal use of talc-based body powder is *possibly carcinogenic to humans (Group 2B)*.

Inhaled talc not containing asbestos or asbestiform fibres is *not classifiable as to its carcinogenicity (Group 3)*.

6.4 Rationale

In making this evaluation the Working Group considered the human and animal evidence as well as evidence regarding the potential mechanisms through which talc might cause cancer in humans.

The Working Group found little or inconsistent evidence of an increased risk for cancer in the studies of workers occupationally exposed to talc. The studies of talc miners and millers were considered to provide the best source of evidence, but no consistent pattern was seen. One study observed an excess risk for lung cancer among miners, but confounding from exposure to other carcinogens made it difficult to attribute this to talc and no excess risk was seen in millers. Other studies also found no increased cancer risk or no higher risk with increasing cumulative exposure. Overall, these results led the Working Group to conclude that there was *inadequate evidence* from epidemiological studies to assess whether inhaled talc not containing asbestos or asbestiform fibres causes cancer in humans.

For perineal use of talc-based body powder, many case–control studies of ovarian cancer found a modest, but unusually consistent, excess in risk, although the impact of bias and potential confounding could not be ruled out. In addition, the evidence regarding exposure–response was inconsistent and the one cohort study did not provide support for an association between talc use and ovarian cancer. Concern was also expressed that

exposure was defined in a variety of ways and that some substances called talc may have contained quartz and other potentially carcinogenic materials. A small number of Working Group members considered the evidence to be inadequate. Despite these reservations, the Working Group concluded that the epidemiological studies taken together provide *limited evidence* of an association between perineal use of talc-based body powder and an increased risk for ovarian cancer.

In one study of rats that inhaled talc, an excess incidence of malignant lung tumours was seen in females. The same study observed an excess incidence of pheochromocytomas in the adrenal medulla in both sexes, but the Working Group was divided as to whether these rare tumours could be attributed to exposure to talc. Other studies in rats and mice using different routes of administration did not find an excess of cancer, and two studies in rats were considered to be inadequate for evaluation. Based on the one positive study, the Working Group found that there was *limited evidence* of carcinogenicity of inhaled talc in experimental animals. There was no agreement within the Working Group as to whether the evidence on pheochromocytomas should be taken into account in the evaluation of animal data.